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13. ABSTRACT *(Maximum 200 words)*

Major advances in the physics and technology for the production and utilization of laser-polarized ^{3}He and ^{129}Xe have resulted from this DARPA-sponsored research. A high-capacity polarizer and accumulator for ^{129}Xe has been developed and has been successfully transferred to the commercial sector. We have developed a powerful new method for imaging the three-dimensional distribution of the electronic spin polarization of the alkali-metal vapors used for spin-exchange optical pumping of ^{3}He and ^{129}Xe. Absolute electronic spin polarizations are obtained. We have demonstrated that the intrinsic spin-exchange efficiency for polarizing ^{3}He is ten times better with optically pumped K vapor than with the currently used Rb vapor. Using equipment with key technological features resulting from this work, collaborators at the University of Virginia Medical School now make routine use of ^{3}He lung images of patients scheduled for lung resection surgery.

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William Harper 19 Feb. 1999

PI - Signature Date

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INTRODUCTION

In most medical applications of magnetic resonance imaging (MRI), images of body tissues are obtained by mapping the density and relaxation times of hydrogen nuclei. However, certain portions of the body, most notably the lungs, have remained difficult to image using conventional MRI. Information about lung function has been even more difficult to obtain with presently available radiological techniques. A new implementation of MRI using *laser-polarized* noble gases has recently been demonstrated[1,2], wherein lasers are used to enhance the MR signal from noble gases such as ^{3}He and ^{129}Xe, making them easily observable in a conventional MRI scanner. In-vivo experiments had just yielded spectacular magnetic resonance images of the lungs of laboratory animals at the time this grant began a few years ago, and now hundreds of humans have been imaged, and the success rate of lung resection operations at the University of Virginia Medical School at Charlottesville has been improved as a result of the excellent ^{3}He lung diagnostics available before commencement of the operations. This technology will provide functional information that can be important in evaluating and treating pulmonary embolisms, emphysema, asthma, lung cancer and a wide variety of respiratory problems.

Magnetic resonance imaging with laser-polarized noble gases has been made possible by years of basic physics research in the areas of optical pumping and spin exchange[3], largely supported by AFOSR with more recent assistance by DARPA. Optical pumping uses circularly polarized light, most often from a laser, to create a large electron spin polarization in a vapor of rubidium or similar atoms. In a collision with a noble gas atom, the electron spin of the rubidium atom can be transferred to the nuclear spin of a noble-gas atom. Extremely large nuclear polarizations can be obtained on time scales ranging from minutes to a few hours. With Titanium:Sapphire lasers and, more recently, high-power AlGaAs laser diode arrays, it is possible to polarize nuclei in substantial quantities of gas (a few liters at STP). This is enough for use in magnetic resonance imaging of human lungs.

In magnetic resonance imaging, an image is reconstructed from the radio waves produced by precessing nuclear magnetic moments. For images of human beings, the precessing moments are almost always protons, the nuclei of hydrogen atoms. However, the radio signals from a spin-up nucleus completely cancels the radio signals from a spin-down nucleus, and under normal MRI conditions, the relative excess of spin-up over spin-down protons, that is, the spin polarization, is very small, typically only a few parts per million even in several-tesla magnetic fields. Consequently, the MRI signal per proton is nearly one million times smaller than the maximum possible value. Conventional proton MRI is feasible with these small signals because the human body contains such a high density of protons. By contrast, optical pumping and spin exchange produce noble gas nuclear polarizations of order 1 – close to the maximum possible value. The magnetic resonance signal per noble gas nucleus is nearly one million times larger than the signal per proton in conventional MRI. Even though the density of nuclei in a gas is one thousand times smaller than the density of protons in tissue, the huge increase in polarization more than compensates for the fewer nuclei, and very bright images of laser-polarized gas can be obtained.

The first gas images, of the excised lungs of a mouse, were made in 1994 with a few

cc's of laser-polarized ^{129}Xe by a team of researchers from Princeton University and the State University of New York at Stony Brook[1]. Based on this work, US Patents 5,789,921 and 5,789,953 for in-vivo imaging with laser-polarized gases were awarded to our group at Princeton and our collaborators at Stony Brook. The patent is jointly owned by the two universities, and has been exclusively licensed to a small startup company, Magnetic Imaging Technologies, Inc., based in Durham, North Carolina. and largely staffed by recent graduates of Princeton University. Further collaboration between Princeton and researchers at Duke University[3] yielded the first images made with laser-polarized ^{3}He; the first lung images of a living guinea pig were reported early in 1995. A team from Princeton and Duke Universities[6] produced the first human lung image at the Duke Medical School on September 18, 1995.

MR imaging with laser-polarized noble gases offers a wide variety of possible clinical applications. The large non-equilibrium polarizations allow rapid imaging techniques to be used. Presently, a single "slice" of a human lung can be imaged in much less than one second, so real-time imaging of lung function is possible for the first time. The high resolution offered by the technique and the intrinsic three-dimensional nature of MRI means that areas of compromised lung function can be localized to a much higher degree than presently possible. Current clinical techniques involve the use of inhaled radioactive ^{133}Xe (a gamma emitter) to produce a two-dimensional projection image of the lung with resolutions on the order of 1 cm $\times$ 1 cm. The technique is frequently combined with radioactive ^{99}Tc, injected intravenously and imaged in a similar manner. By contrast, the first fully three dimensional human images obtained with laser-polarized ^{3}He had a resolution of 3mm $\times$ 3mm without any optimization, and current resolutions are substantially better.

While initial experiments have concentrated on imaging in the gas phase, laser-polarized ^{129}Xe offers the further possibility of imaging the blood and tissues as well. Xenon is highly soluble in tissue (especially fatty components) and will dissolve in the blood at levels of order 20% of its concentration in the gas phase. The polarization of ^{129}Xe survives for periods on the order of 10 seconds in human blood, so imaging of ^{129}Xe in almost any desired portion of the body should be feasible. Dissolved ^{129}Xe has a precession frequency that is easily distinguished from the gas-phase frequency, so gas-phase and tissue images can be recorded separately. Detection of pulmonary embolisms (blood clots in the lung), a condition that contributes roughly 200,000 deaths per year in the United States, is envisioned as a procedure which could make excellent use of this type of imaging. Other diagnostic possibilities are almost certain to arise once large-scale clinical research commences. Lung function is an important concern for the DoD in many areas, including lung function of aviators at high altitudes, deep sea divers, and chemical warfare environments.

Thus far, noble gas MRI experiments have made use of commercial MRI scanners which have been retuned to the noble gas precession frequency (a relatively straight-forward and inexpensive task). However, because the signal to noise ratio of the MR signal from laser-polarized noble gases is *independent* of magnetic field strength, imaging with much smaller fields will be possible. A dedicated MRI unit for noble gas imaging would be small, inexpensive, and easily portable.

BODY

Clinical trials of lung imaging with ^{3}He have now begun in earnest. The trials are being managed by Nycomed Amersham, an international healthcare company, and Magnetic Imaging Technologies, Inc. (MITI), a small startup company whose current President, Dr. Bastiaan Driehuys, completed his education at Princeton University with support by this grant. Excellent equipment for polarizing both ^{3}He and ^{129}Xe gas has been developed by MITI, and the research supported by DARPA at Princeton has been a factor in their success. Current MITI polarizers produce ^{129}Xe with about 20% nuclear spin polarization and ^{3}He with 40%. There seems to be no fundamental reason to keep the ultimate polarizations of both isotopes from approaching 100 %, with concomitant gains in clinical effectiveness.

The most important advances resulting from this DARPA grant are described in detail in the publications of APPENDIX B, but we will summarize them here. The first demonstration of the utility of ^{3}He for biological imaging of the lungs of a sacrificed guinea pig was demonstrated by a team of researchers from Duke University and Princeton University at the Center for In-Vivo Spectroscopy at Duke University in 1995. This was soon followed by in-vivo lung images of a guinea pig by the same team in 1996, and by the first in-vivo image of the lungs of human volunteers a few months later.

Also in 1996, Dr. Bastiaan Driehuys and his collaborators from Princeton University demonstrated an apparatus to polarize large quantities of ^{129}Xe gas in a flowing gas stream, and to accumulate the polarized ^{129}Xe in the form of xenon ice in cold trap at liquid nitrogen temperatures. This device has been patented in the United States and abroad. The patent is owned by Princeton University and has been exclusively licensed to MITI.

In 1996, Dr. Saam and collaborators made the first quantitative studies of "edge enhancement" of magnetic resonance images made with laser-polarized ^{3}He gas. This is an image aberration, analogous to classical optical aberrations like coma or astigmatism, which is due to the hindered diffusion of spin-polarized noble-gas atoms at non relaxing boundaries. Largely due to research supported by DARPA, edge-enhancement phenomena are now well understood both experimentally and theoretically.

In 1997 Professor Happer and his colleague and former student Professor Walker of the University of Wisconsin, published a review of spin-exchange optical pumping and some of its applications in *Reviews of Modern Physics*. Frequently cited, this paper has helped to clarify what is well understood and what needs further research in this area.

In 1997 Professors Cates and Happer with their colleagues Dr. Mugler and Dr. Brookeman at the University of Virginia Medical School published the first images of human subjects with chronic obstructive pulmonary disease. The ventilation defects stood out dramatically in the ^{3}He images.

In 1997, Dr. Young and his colleagues demonstrated an effective way to measure the distribution of electronic spin polarization of the alkali-metal atoms in spin-exchange optical pumping cells. The method is closely related to MRI and uses a magnetic field gradient to map spatial variations into frequency variations. Both relative and absolute polarizations can be readily measured by this new method. An interesting finding of this work was that the distribution of alkali-metal atoms between the spin sublevels of the ground state was very nearly the spin-temperature distribution.

In 1997, Professor G. A. Johnson with collaborators from Princeton showed that the signal-to-noise ratio of MRI with ^{3}He was so high that the time dependence of lung ventilation could be measured in snapshots only fractions of seconds apart.

Also in 1997 Dr. Karen Sauer demonstrated for the first time that enough laser-polarized ^{129}Xe could be produced by the flowing systems that several milliliters of hyper-polarized liquid xenon could be produced. In contrast to solidified xenon, where holding fields of at least 500 Gauss are needed to prevent rapid spin relaxation, the relaxation time in the liquid, about 20 minutes, is the same in the earth's field of about 0.5 Gauss as in much higher magnetic fields. Soon thereafter, Dr. Fitzgerald and Dr. Sauer showed that the high spin polarization of the liquid ^{129}Xe could be transferred to the nuclei of substances dissolved in the liquid xenon. Many non-polar substance, for example, cyclo-hexane, CS_2, etc., are readily soluble in liquid xenon. Large enhancements of the nuclear spin polarizations of ^{1}H ^{2}H and ^{13}C were observed.

In 1998, a series of papers were published by Dr. Baranga, Dr. Appelt and their collaborators on the physics of imaging the electronic spin polarization of dense alkali-metal vapors. One of the unusual phenomena discovered in the course of these investigations was "light narrowing" of the magnetic resonance lines, a result of the suppression of spin-exchange broadening in highly spin-polarized alkali-metal vapors.

Finally, in 1998 Dr. Baranga and his colleagues showed that the intrinsic spin-exchange efficiency of potassium vapor is about ten times larger that that of rubidium vapor. Although potassium is more difficult to work with than rubidium because higher temperatures are needed to generate adequate vapor pressures for absorbing the laser pumping light, one could in principle produce the same volumes of hyperpolarized ^{3}He as now done with rubidium as the spin-exchange partner with potassium and a laser of one tenth the power.

CONCLUSIONS

The aim of this, work as outlined in the **Statement of Work** attached as Appendix A, was to develop as rapidly as possible the capability to produce large amounts of nuclear spin-polarized ^{129}Xe and ^{3}He gas for magnetic resonance imaging of humans and for other applications. This promising new diagnostic method uses conventional magnetic resonance imaging machines, along with laser-polarized ^{129}Xe and ^{3}He gas, to make images of human lungs and other body cavities. Xenon is so soluble in blood and tissue that it will be possible to image other organs like the brain with laser-polarized ^{129}Xe. The research has been successful, and some of the highlights are:

- The first ^{3}He images of human lungs were obtained in collaboration with the Radiology Department of the Duke University Medical School on September 19, 1995.
- We have invented and demonstrated an effective method to image the spatial distribution of the absolute spin polarization of the optically pumped alkali-metal atoms in glass pumping chambers. The method uses a magnetic field gradient to map the frequency of radiofrequency resonances into the spatial distribution of spin polarization. The radiofrequency resonances are detected by observing the resulting modulation of a weak laser probe beam that passes through the cell.
- Together with the startup company Magnetic Imaging Technologies, Inc., and the diode laser manufacturer, Opto Power, Inc., we have developed a high power, fiber-coupled diode laser array that has proven practical and reliable for spin-exchange optical pumping. This is the work proposed in Item 1. of the Statement of Work, "Diode lasers."
- A cryogenic accumulator for laser-polarized ^{129}Xe has been successfully developed to produce the large amounts (liters) of ^{129}Xe needed for diagnostic studies of the human body. The accumulator is very similar to the device proposed in Item 2. of the Statement of Work, "Large-volume source of spin polarized Xe-129." A United States patent for the device has been issued to Princeton University and licensed to Magnetic Imaging Technologies, Inc.
- The first ^{129}Xe images of a human lung were obtained in collaboration with the Radiology Department of the University of Virginia in the spring of 1996. This kind of experiment was proposed in Item 3. of the Statement of Work, "Magnetic resonance imaging with Xe-129."
- Stimulated by our work, the first international workshop on inert gas imaging was held in Les Houches, France during the fall of 1996. A followup, second international conference will be help in Les Houches in June of 1999.
- Seventeen publications in refereed journals have been fully or partially supported by this DARPA grant.

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PERSONNEL

The following personnel received full or partial support from the grant:

Dr. William Happer, Professor of Physics and Principal Investigator

Dr. Gordon Cates, Professor of Physics

Dr. Albert Young, Assistant Professor of Physics

Dr. Bastiaan Driehuys, Research Associate

Dr. Brian Saam, Research Associate

Dr. Eli Miron, Research Associate

Dr. Andrei Baranga, Research Associate

Dr. Stephan Appelt, Research Associate

Dr. David Levron, Research Associate

Ms. Karen Sauer, Graduate Student, (now Dr. Karen Sauer and the recipient of the Chateaubriand Fellowship of the French Government for postgraduate research in Paris)

Mr. Chris Erickson, Graduate Student

Mr. Dan Walter, Undergraduate Summer Research Student, (now a Graduate Student with our research group after returning from a Marshall Scholarship at Oxford, England)

<u>APPENDIX A</u>

Statement of Work
for ARPA Grant DAMD 17-94-J-4469

Laser Spin-Exchange Polarized ^{3}He and ^{129}Xe for Diagnostics of Gas-Permeable Media with Nuclear Magnetic Resonance Imaging

1. **Diode lasers.** We will optimize the design of spin-exchange optical pumping systems for inexpensive diode laser arrays. The important issues are:
   (a) The large spectral linewidth ($\approx$ 2 nm FWHM) of the diode lasers. This makes it necessary to use pumping chambers with high gas pressures, typically several atmospheres or more, to provide enough pressure broadening of the atomic absorption line of the alkali-metal atoms to utilize most of the laser light.
   (b) We will assess the long-term reliability of diode laser arrays for spin-exchange optical pumping. For pumping the vapor of rubidium metal, GaAlAs diode material is needed. In the past, the tendency of the Al to oxidize at the end facets and the related propagation of dark line defects have limited the lifetime of GaAlAs diode lasers. However, major improvements in processing may have resolved these problems. If GaAlAs laser lifetime should be a serious issue, there are good reasons to expect much longer lifetimes from aluminum-free materials like GaSbAs, which can be grown by MOVCD. The operating wavelengths of aluminum-free lasers are too long to pump Rb vapor, but they would be an excellent match for Cs vapor.
2. **Large-volume source of spin polarized Xe-129.** So far, only He-3 is available in sufficient quantities (liters) for magnetic resonance imaging of human lungs. We will develop large volume sources of Xe-129, which is of interest because of its much greater solubility in human tissue than He-3, and because there is an inexhaustible, readily recoverable supply from the atmosphere. The issues we must address here are:
   (a) The spin-exchange and spin destruction cross sections of Xe-129 with alkali-metal atoms are some five orders of magnitude bigger than those for He-3. Other things being equal, this means that Xe-129 can be polarized five orders of magnitude more quickly than He-3. Unfortunately, Xe-129 is also five orders of magnitude more potent in destroying the spin of the alkali-metal atoms than He-3. Selecting the optimum concentration of Xe-129 and other gases in the optical pumping chamber is therefore crucial to allow fast pumping while maintaining adequate spin polarization of the alkali-metal atoms.
   (b) It is more difficult to store spin polarized Xe-129 for long periods of time than is the case for He-3 gas, which can be kept polarized at room temperatures for many hours. We expect to be able to solve this problem by developing deuterated wall coating materials for the cells that contain Xe-129. Work in our laboratory has shown that most of the spin relaxation of Xe-129 is due to interactions with the nuclear magnetic moments of protons of hydrogenated wall materials. Since deuterons have a much smaller magnetic moment than protons, they will cause less spin depolarization.

(c) A very convenient way to maintain spin polarized Xe-129 for long periods of time is to freeze it at liquid nitrogen temperatures or below, where it has completely reproducible spin relaxation times of many hours. We will incorporate cryogenic storage of Xe-129 in our systems.

3. **Magnetic resonance imaging with Xe-129.** Although Xe-129 was used in the very first magnetic resonance images with laser-polarized gases – a mouse lung imaged in a collaboration between our Princeton group and a group at the State University of New York at Stony Brook –the most spectacular recent images have been obtained with He-3, which until now has been available in much larger volumes than Xe-129. With the success of our efforts to make much larger amounts of spin-polarized Xe-129, we will use it to image laboratory animals and perhaps humans. Xenon gas is very soluble in blood, and there is a good possibility that enough Xe-129 will dissolve in the blood to permit magnetic resonance imaging of body tissue. This work will be done in collaboration with enthusiastic research partners at the medical schools of Duke University, the University of Virginia, the University of Texas at San Antonio, and Vanderbilt University.

APPENDIX B

REFEREED PUBLICATIONS RESULTING FROM DARPA RESEARCH

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